reserve the right to purse any non-elected, canceled, or otherwise unclaimed subject matter in continuing applications.

The above-made amendments are fully supported in the specification of the instant application as originally filed and do not constitute new matter. Applicants believe that the amendments address the concerns of the Examiner. Accordingly, entry of the foregoing amendments and remarks are respectfully requested. Should the Examiner determine that there are remaining issues, the Examiner is invited to contact the undersigned or Leon F. Hebert at the below indicated telephone number to discuss such issues.

Respectfully submitted,

Date February 25, 2002

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Enclosure

APPENDIX A: MARKED-UP AMENDED CLAIM 2

U.S. PATENT APPLICATION SERIAL NO. 09/385,9218 (ATTORNEY DOCKET NO. 10624-048)

2. **(Amended)** A method according to claim 1, wherein the HECT E3 upiquitin ligase WW domain comprises the sequence

GPLPXGWEX$_3$tttGtXYYhXHNTtTTtWXtPt (SEQ ID NO:2)

wherein each t is an independently selected polar amino acid residue [(*e.g.*, S, H, P, D, E, T or Y)], h is a hydrophobic residue [(*e.g.*, I, V, L or M)] and each X is an independently selected amino acid residue.

APPENDIX B: PENDING CLAIMS

U.S. PATENT APPLICATION SERIAL NO. 09/385,9218 (ATTORNEY DOCKET NO. 10624-048)

1. A method for screening for an agent that modulates BMP-mediated signaling, comprising the steps of:

(a) contacting

(i) a first polypeptide comprising a HECT E3 ubiquitin ligase WW domain; SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13, or a variant thereof in which the ability of the polypeptide to bind to a Smad protein is not substantially diminished relative to the HECT E3 ubiquitin ligase;

(ii) a second polypeptide comprising a Smad PY motif; SEQ ID NO:14, 15, 16, 17, 20, 21, 22, 23, 24, or 25, or a variant thereof in which the ability of the polypeptide to bind to an E3 ubiquitin ligase is not substantially diminished relative to a native Smad protein comprising the PY motif; and

(iii) a candidate agent; under conditions that permit a detectable level of binding of the first polypeptide to the second polypeptide in the absence of candidate agent;

(b) determining a level of binding of the first polypeptide to the second polypeptide; and

(c) comparing the level of binding to a control level of binding of the first polypeptide to the second polypeptide in the absence of candidate agent, and therefrom determining whether the candidate agent modulates BMP-mediated signaling.

2. A method according to claim 1, wherein the HECT E3 upiquitin ligase WW domain comprises the sequence

$GPLPXGWEX_3tttGtXYYhXHNTtTTtWXtPt$ (SEQ ID NO:2)

wherein each t is an independently selected polar amino acid residue, h is a hydrophobic residue and each X is an independently selected amino acid residue.

3. A method according to claim 1, wherein the Smad PY motif comprises the sequence Ser/Thr-Pro-Pro-Pro-Pro/Ala/Gly-Tyr (SEQ ID NO:15), wherein Ser/Thr is an

amino acid residue that is serine or threonine and Pro/Ala/Gly is an amino acid residue that is selected from the group consisting of proline, alanine and glycine.

4. A method according to claim 3, wherein the Smad PY motif comprises the sequence TPPPAY (SEQ ID NO:16) or TPPPGY (SEQ ID NO:18).

5. A method according to claim 1, wherein the candidate agent is a small molecule within a combinatorial library.

6. A method according to claim 1, wherein the first polypeptide is immobilized on a solid support and the second polypeptide comprises a tag.

7. A method according to claim 1, wherein the second polypeptide is immobilized on a solid support and the first polypeptide comprises a tag.

8. A method according to claim 6 or claim 7, wherein the tag is biotin or a radioactive group.

9. A method according to claim 1, wherein the level of binding is determined via a two-antibody sandwich assay.

10. A method according to claim 1, wherein the level of binding is determined via a competitive assay.

54. A method according to claim 2, wherein each t is selected from the amino acid residue group consisting of S, H, P, D, E, T and Y.

55. A method according to claim 2, wherein each h is selected from the hydrophobic residue group consisting of I, V, L and M.